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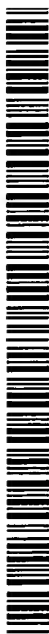


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(54) Title: ANTI-CANCER COMPOSITION COMPRISING DMXAA OR RELATED COMPOUND

(57) Abstract: The present invention relates to the use of compounds such as compounds of the xanthenone acetic acid class such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA) for the treatment of cancer, wherein the compounds are administered gastrointestinally, preferably orally. More particularly, the invention is concerned with the use of such compounds, wherein the compound is delivered to the site of action in the patient to be treated in two or more doses.

ANTI-CANCER COMPOSITION COMPRISING DMXAA OR RELATED COUMPOUND

The present invention relates to pharmaceutical compositions and their use in therapy, particularly in the treatment of cancers. In particular, the present invention relates to formulations of anticancer compositions which can be delivered gastrointestinally, for example orally, and to a method of treatment of cancer, in which the anticancer compositions are delivered gastrointestinally, such as orally. More in particular, the present invention relates to the progressive or sequential delivery or release of gastrointestinally administered compounds of the class having the formula (I) as defined below, for example compounds of the xanthenone acetic acid class having the formula (II) as defined below, such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA).

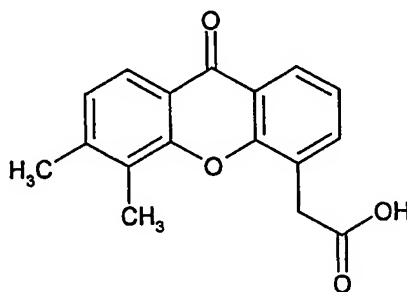
The use of drugs in systemic chemotherapy has provided effective management of some cancer types. For example, systemic chemotherapy has been used successfully in the treatment of cancers of the colon-rectum, oesophagus, liver, pancreas, kidney and skin. Prolonged periods of therapy may be required in cancer patients to control tumour growth and, in some instances, prevent the growth of secondary malignancies. Anti-cancer drugs having poor bioavailability are required in high doses to maintain their efficacy. As a result the continuing administration of high dosages of systemic therapeutic agents may be required to provide efficacious amounts of chemotherapeutic agents.

A major problem with systemic chemotherapy for the treatment of cancer is that the systemic dose levels required for controlling tumour growth frequently result in unacceptable systemic toxicity. For example, although paclitaxel (TaxolTM, Bristol Myers Squibb) has been used systemically with efficacy in treating several human tumours, including ovarian, breast, and non-small cell lung cancer, maintenance of sufficient systemic levels for tumour efficacy has been associated with severe, in some cases "life-threatening" toxicity (Sarosy and Reed, J. Nat. Med. Assoc. 85(6):427-431 (1993)).

There has been an increasing trend toward the development of oral systemic chemotherapeutic agents having improved efficacy and bioavailability for the treatment of patients with a variety of malignancies. Chemotherapy administered gastrointestinally, provides social, economic and medical benefits. For example, the cost of treatment is usually far lower compared to intravenous administration and gastrointestinal administration (particularly oral or rectal administration) is more convenient for patients, permitting them to remain at home while taking their medications and eliminating the

need for venous access, which may require the presence of a physician and/or nurse and/or a prolonged stay in hospital. However, despite the desirability of developing an orally active treatment, to date there has been little success in doing so for many otherwise useful anticancer agents.

In particular, to date, there has been no successful demonstration of tumour treatment using gastrointestinally, for example orally, administered xanthenone acetic acid compounds, such as DMXAA (5,6-dimethylxanthenone-4-acetic acid). DMXAA is an effective drug with an anti-vascular action. DMXAA is represented by the following formula:



Phase I clinical trials of DMXAA have recently been completed, with dynamic MRI showing that it induces a significant reduction in tumour blood flow at well-tolerated doses. DMXAA is thus one of the first antivascular agents for which activity (irreversible inhibition of tumour blood flow) has been documented in human tumours. These findings are in agreement with preclinical studies using tumours or human tumour xenografts which showed that its antivascular activity produced prolonged inhibition of tumour blood flow leading to extensive regions of haemorrhagic necrosis within the tumour.

Preclinical studies have demonstrated the utility of combining DMXAA with other agents including thalidomide, radiation therapy, bioreductive agents, cytotoxic drugs and radioimmunotherapy. However, typically, the administration of DMXAA in preclinical trials has been restricted to intraperitoneal (i.p) and intravenous (i.v) injection. Orally administered DMXAA has shown only limited antitumour activity. Zhao et al (Cancer Chemother Pharmacol. 2002 Jan;49(1):20-6) describes the administration of DMXAA orally and reports that the antitumour effect, as measured by delay in tumour growth achieved with a single dose of orally administered DMXAA is low compared to that achieved when DMXAA was administered intraperitoneally. Indeed, no cures were

obtained using the orally administered DMXAA compared to 40% for intraperitoneal administration. Moreover, repeated dosing of DMXAA administered intraperitoneally over a 24 hour period was not found to be superior to administration of a single dose.

5 There is therefore a need to provide a composition and method of use for the treatment of solid tumours with chemotherapeutic agents such as DMXAA that avoids high systemic levels of the agent and associated toxicities and which offers the social, medical and economic benefits of gastrointestinal delivery.

10 Summary of the Invention

It has now surprisingly been found that, contrary to the teaching of the prior art, by administering compounds having the formula (I) as defined below in sequential
15 gastrointestinally administered doses, potentiation of the antitumour activity of compounds of formula (I) compared to that achieved when a single dose is administered is nevertheless achieved. In particular administration of compounds of formula (I) as defined below such as DMXAA administered in a dosing regimen of a first high oral dose (approximately corresponding to the maximum tolerated dose) followed by one or
20 more, preferably two or more, further oral doses within a 24 hour time frame has surprisingly been found to provide a therapeutic gain, as compared to the oral administration of the maximum tolerated single dose (MTD) against sub-cutaneously established colon tumour, without a concomitant increase in host toxicity.

The finding that such a therapeutic gain could be achieved using a sequential oral regime
25 without associated serious toxicity was particularly surprising given that, using the area under concentration curve associated with the treatment regime as a predictor of toxicity, unacceptable side effects/toxic effects would be predicted. However, no such effects were seen, suggesting that, without being limited to any one explanation, toxicity of DMXAA and other compounds of the class of compounds of Formula (I) is related to
30 maximum concentration and not the area under the concentration-time curve.

The present inventors findings thus enable the effective treatment of tumours using gastrointestinally administered, preferably orally administered DMXAA and other
35 compounds of Formula (I) without high levels of toxicity and side-effects.

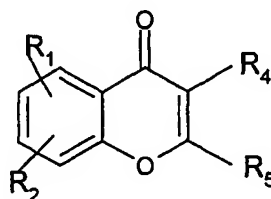
As described below, the present inventors have found that delay in growth of subcutaneous tumours can be induced using sequential oral administration of a xanthenone-4-acetic acid derivative. The present inventors findings thus enable the

effective treatment of tumours using gastrointestinally administered DMXAA without high levels of toxicity and side-effects.

Accordingly, in a broad aspect, the present invention relates to the sequential gastrointestinal administration of a composition comprising a compound having the formula (I) as defined below for use in controlling tumour growth.

Thus, in a first aspect, the present invention provides a method for modulating neoplastic growth, which comprises gastrointestinally administering to a mammal, including a human, in need of treatment an effective amount of a compound of the formula (I):

Formula (I)



or a pharmaceutically acceptable salt or ester thereof, wherein said effective amount is delivered to its site of action in the mammal in two or more doses;

wherein:

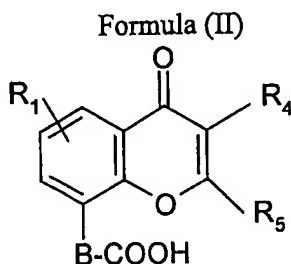
(a) R_4 and R_5 together with the carbon atoms to which they are joined, form a 6-membered aromatic ring having a substituent $-R_3$ and a radical $-(B)-COOH$ where B is a linear or branched substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated, and wherein R_1 , R_2 and R_3 are each independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, CF_3 , CN, NO_2 , NH_2 , OH, OR, $NHCOR$, $NHSO_2R$, SR, SO_2R or NHR , wherein each R is independently C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy; or

(b) one of R_4 and R_5 is H or a phenyl radical, and the other of R_4 and R_5 is H or a phenyl radical which may optionally be substituted, thenyl, furyl, naphthyl, a C_1-C_6 alkyl, cycloalkyl, or aralkyl radical; R_1 is H or a C_1-C_6 alkyl or C_1-C_6 alkoxy radical; R_2 is the radical $-(B)-COOH$ where B is a linear or branched substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated.

Where the radical $-(B)-COOH$ is a substituted C_1-C_6 alkyl radical, the substituents may be alkyl, for example methyl, ethyl, propyl or isopropyl, or halide such as fluoro, chloro or bromo groups. A particularly preferred substituent is methyl.

5

In one embodiment of the first aspect of the invention, the compound of the formula (I) as defined above is a compound of the formula (II),

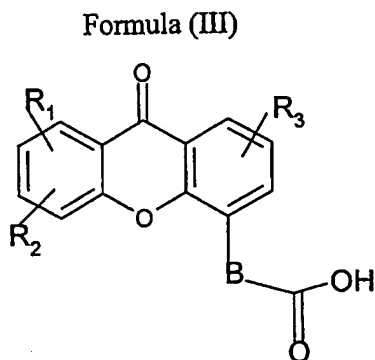


10

where R_1 , R_4 , R_5 and B are as defined above for formula (I) in part (b).

15

In a preferred embodiment of the first aspect of the invention, the compound of formula (I) as defined above is a compound of the formula (III)



20

wherein R_1 , R_2 and R_3 are each independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, CF_3 , CN, NO_2 , NH_2 , OH, OR, $NHCOR$, $NHSO_2R$, SR, SO_2R or NHR , wherein each R is independently C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy;

25

wherein B is as defined for formula (I) above;

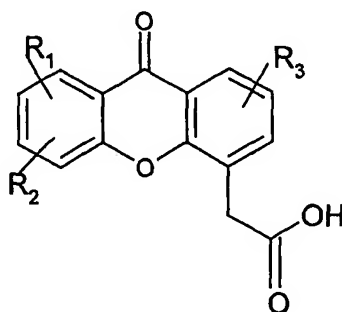
and wherein in each of the carbocyclic aromatic rings in formula (I), up to two of the methine (-CH=) groups may be replaced by an aza (-N=) group;

5 and wherein any two of R₁, R₂ and R₃ may additionally together represent the group -CH=CH-CH=CH-, such that this group, together with the carbon or nitrogen atoms to which it is attached, forms a fused 6 membered aromatic ring.

Preferably, the compound of formula (III) is a compound of the formula (IV):

10

Formula (IV)

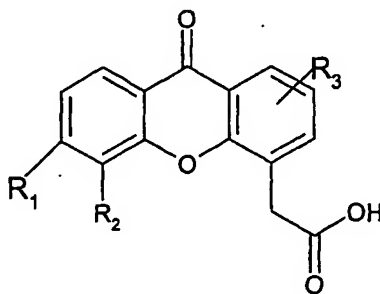


wherein R, R₁, R₂ and R₃ are as defined for formula (III).

15 In a preferred embodiment of the compound of formula (IV), R₂ is H, one of R₁ and R₃ is selected from the group consisting of C₁-C₆ alkyl, halogen, CF₃, CN, NO₂, NH₂, OH, OR, NHCOR, NHSO₂R, SR, SO₂R or NHR, wherein each R is independently C₁-C₆ alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy, and the other of R₁ and R₃ is H.

20 Preferably, the compound of formula (IV) is of the formula (V):

Formula (V)



wherein R, R₁, R₂ and R₃ are as defined for formula IV.

Most preferably, the compound of formula (IV) is 5,6-dimethylxanthenone 4 acetic acid (DMXAA).

5

In a further aspect, the present invention provides a compound of formula (I) as defined above for use in the prevention or treatment of cancer; wherein the compound is provided in a composition for sequential gastrointestinal administration, and wherein, in use, an effective therapeutic amount of said compound is delivered to a site of action over two or more doses.

10

In another aspect, the present invention provides the use of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or ester thereof for the manufacture of a medicament, for gastrointestinal administration, for the modulation of neoplastic growth, wherein, said medicament is delivered to its site of action in the mammal in two or more doses.

15

In preferred embodiments of the invention, the two or more doses are provided as separate dosage forms for sequential administration to the mammal in need thereof, with a time interval between administration of the doses.

20

In alternative embodiments of the invention, the two or more doses are provided in a single dosage form, such as a controlled release formulation, for administration to the mammal in need thereof, which, in use releases the individual doses at different times, with a time interval between successive releases of doses.

25

In preferred embodiments of the invention, the route of gastrointestinal administration is oral administration.

30

As used herein the phrase "preparation of a medicament" includes the use of a compound of the invention directly as the medicament in addition to its use in a screening programme for the identification of further agents or in any stage of the manufacture of such a medicament.

35

By "therapeutically effective amount" is meant an amount of the compound formula (I) or one of its salts that when administered gastrointestinally, preferably orally, alone or in combination formulation such that the compound is delivered to a site of action in two or

more doses is effective to treat the various disorders for which the compound having formula (I) as defined above has been disclosed as a useful treatment.

5 The compound of formula (I), or pharmaceutically acceptable salt or ester thereof may be administered in any suitable form. However, for use according to the present invention the compound of formula (I) or a pharmaceutically acceptable salt or ester thereof is preferably presented as a pharmaceutical formulation. Pharmaceutical formulations comprise the active ingredient (that is, the compound of formula (I) or a pharmaceutically acceptable salt or ester thereof) together with one or more
10 pharmaceutically acceptable carriers therefor and optionally other therapeutic and/or prophylactic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof.

15 Accordingly, in a further aspect there is provided a pharmaceutical formulation comprising a compound of formula (I) as defined above or a pharmaceutically acceptable salt or ester thereof wherein said pharmaceutical formulation is adapted for gastrointestinal, preferably oral, administration. Preferably said compound and/or pharmaceutical formulation is adapted for delivery of the active compound to its site of
20 action in a mammal in need thereof in two or more doses, preferably two or more discrete doses.

In one preferred embodiment, said pharmaceutical formulation comprises said compound at an amount which, when administered as a single oral dose, is therapeutically
25 ineffective, but, when the same total amount is administered by providing two or more sequential smaller oral doses, is therapeutically effective. Suitably, the smaller doses themselves are not effective if administered individually but are effective when administered sequentially to make up the total amount.

30 By "therapeutically ineffective amount" is meant an amount of the compound of the invention or one of its salts that, when administered as a single dose, is not effective to treat the various disorders for which the compound having formula (I) as defined above has been disclosed as a useful treatment or is such that, although a therapeutically effective result may be achieved, the amount is greater than the maximum tolerated dose
35 and/or the associated side effects are unacceptable i.e. not acceptable to the patients, the doctor(s) in charge of treatment or regulatory bodies such as the US Food and Drug Administration.

Said sequential doses are separated by a time interval, the calculation of which is preferably based on the plasma half-life ($t_{1/2}$) of the drug. The time interval is preferably approximately equal to one half-life of the drug, for example in the range 50% $t_{1/2}$ to 150% $t_{1/2}$, preferably in the range 70% $t_{1/2}$ to 130% $t_{1/2}$, more preferably in the range 80% $t_{1/2}$ to 120% $t_{1/2}$, even more preferably in the range 90% $t_{1/2}$ to 110% $t_{1/2}$, most preferably in the range 95% $t_{1/2}$ to 100% $t_{1/2}$. For example, the time interval is preferably greater than 1 hour, preferably greater than 2 hours, more preferably greater than 3 hours. Preferably said doses are separated by a time interval of less than 24 hours, for example, 4 hours, 6 hours or 8 hours.

In a further preferred embodiment of the invention, the pharmaceutical formulation is a controlled release formulation, wherein, in use, said formulation releases two or more doses, preferably at least two or more doses separated by a time interval between each dose. Preferably, each of said doses is such that, when administered as a single dose, it would be ineffective, but, when administered in two or more sequential doses is therapeutically effective.

Preferably said doses are released from said controlled release formulation with a time interval as described above for sequential doses. In a preferred embodiment, the time interval is at least one hour, more preferably at least two hours, most preferably at least four hours between doses. In a particularly preferred embodiment, the time interval is between 1 and 6 hours.

In a preferred embodiment, the invention further provides a process for the preparation of a pharmaceutical formulation comprising a compound of formula (I) as defined above wherein said process comprises bringing into association at least one unit dose and, optionally, one or more further unit doses of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or ester thereof with one or more pharmaceutically acceptable carriers therefor, wherein said formulation is adapted for gastrointestinal, preferably oral, administration. Preferably said pharmaceutical formulation is adapted for delivery of the active compound to its site of action in a mammal in need thereof in two or more doses, preferably two or more discrete doses.

In a preferred embodiment, the process comprises bringing into association a first unit dose of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or ester thereof with at least one further unit dose of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or ester thereof and one or more pharmaceutically acceptable carriers therefor wherein, on administration to an individual,

said first unit dose and said further unit doses are released from the formulation in discrete doses separated by a time interval.

5 According to a further aspect of the present invention, there is provided a pharmaceutical pack comprising two or more compartments wherein at least two compartments each house at least one dose each of the compound of formula I as defined above which may be in admixture with one or more of: a pharmaceutically acceptable carrier, diluent or excipient (or combinations thereof), an adjuvant or a pharmaceutically active agent, and wherein each dose of the compound of formula I are for administration
10 in sequential gastrointestinal, preferably oral doses, preferably separated by a time interval. Preferably, said time interval is as described above.

The pack of the present invention may comprise a further compartment which houses a pharmaceutically acceptable carrier, diluent or excipient.

15 Furthermore, the invention also provides a kit comprising in combination for separate or sequential use in modulating neoplastic growth, a first unit dose of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or ester thereof and at least one further unit dose of said compound or pharmaceutically acceptable salt or ester thereof, wherein said first and second unit doses are for gastrointestinal, preferably oral
20 administration.

COMPOUNDS

25 Compounds of formula (I) and (II) may be prepared by methods known in the art. For instance, compounds of formula (I), wherein R₁, R₂, R₃, and R₄ are as defined in part (b) of the definition of formula (I) as recited above, may be prepared using the methods as disclosed in US 4,602,034 (Briet et al), the contents of which are herein incorporated by reference.

30 Compounds of formula (III), (IV) and (V) are known and may be prepared using the methods known in the art. For example, compounds of formula (III), (IV) and (V) and their preparation are described in the following references, the contents of which are herein incorporated by reference:

35 Rewcastle *et al*, Journal of Medicinal Chemistry 34(1): 217-22, January 1991;
Rewcastle *et al*, Journal of Medicinal Chemistry 34(2): 491-6, February 1991;
Atwell *et al*, Journal of Medicinal Chemistry 33(5): 1375-9, May 1990;

Rewcastle *et al*, Journal of Medicinal Chemistry 34(9): 2864-70, September 1991;
Rewcastle *et al*, Journal of Medicinal Chemistry 32(4): 793-9, April 1989

5 DMXAA may be prepared according to the methods described in Rewcastle *et al*,
Journal of Medicinal Chemistry 34(1): 217-22, January 1991, the contents of which are
incorporated herein by reference.

PHARMACEUTICAL SALTS

10 The compounds used in the present invention may be administered as pharmaceutically
acceptable salts. Typically, a pharmaceutically acceptable salt may be readily prepared
by using a desired acid or base, as appropriate. The salt may precipitate from solution
and be collected by filtration or may be recovered by evaporation of the solvent.

15 Pharmaceutically-acceptable salts are well known to those skilled in the art, and for
example include those mentioned by Berge *et al*, in J.Pharm.Sci., 66, 1-19 (1977).
Suitable acid addition salts are formed from acids which form non-toxic salts and include
the hydrochloride, hydrobromide, hydroiodide, nitrate, sulphate, bisulphate, phosphate,
hydrogenphosphate, acetate, trifluoroacetate, gluconate, lactate, salicylate, citrate,
20 tartrate, ascorbate, succinate, maleate, fumarate, gluconate, formate, benzoate,
methanesulphonate, ethanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

When one or more acidic moieties are present, suitable pharmaceutically acceptable base
addition salts can be formed from bases which form non-toxic salts and include the
25 aluminium, calcium, lithium, magnesium, potassium, sodium, zinc, and
pharmaceutically-active amines such as diethanolamine, salts.

The compounds used in the present invention may exist in polymorphic form.

30 In addition, the compounds used in the present invention may contain one or more
asymmetric carbon atoms and therefore exists in two or more stereoisomeric forms.
Where a compound contains an alkenyl or alkenylene group, cis (E) and trans (Z)
isomerism may also occur. The present invention includes use of the individual
stereoisomers of the compound and, where appropriate, the individual tautomeric forms
35 thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional
techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a

stereoisomeric mixture of the agent or a suitable salt or derivative thereof. An individual enantiomer of the compound may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

The present invention also includes use of all suitable isotopic variations of the compound of Formula (I) or a pharmaceutically acceptable salt thereof. An isotopic variation of an compound of the present invention or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the compound and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as 2H , 3H , 13C , 14C , 15N , 17O , 18O , 31P , 32P , 35S , 18F and 36Cl , respectively. Certain isotopic variations of the compound and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as 3H or 14C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., 3H , and carbon-14, i.e., 14C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., 2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compound of the present invention and pharmaceutically acceptable salts thereof this invention can generally be prepared by conventional procedures using appropriate isotopic variations of suitable reagents.

The terms used in the claims encompass one or more of the forms just mentioned.

FORMULATION

The component(s) of the present invention may be formulated into a pharmaceutical composition, such as by mixing with one or more of a suitable carrier, diluent or excipient, by using techniques that are known in the art.

PHARMACEUTICAL COMPOSITIONS

5 The compounds used in the present invention may be administered alone but will generally be administered as a pharmaceutical composition or formulation – e.g. when the components are in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine and will typically comprise any one or more of a pharmaceutically acceptable diluent, carrier, or excipient. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as - or in addition to - the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s), buffers, flavouring agents, surface active agents, thickeners, preservatives (including anti-oxidants) and the like, and substances included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

20 Examples of suitable carriers include lactose, starch, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol and the like. Examples of suitable diluents include ethanol, glycerol and water.

25 Examples of suitable binders include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose and polyethylene glycol.

30 Examples of suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

35 Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

TREATMENT/THERAPY

As with the term "treatment", the term "therapy" includes curative effects, alleviation effects, and prophylactic effects. The treatment/therapy may be on humans or animals.

5

The compounds and compositions may be used to treat any cancer. For example, the compounds, formulations and methods of the present invention may be used to treat malignancy of any type including, for example, cancer of the lung, breast, testes, prostate, gut including colon, ovary, skin, kidney, pancreas, and lymphatic organs, cervix, liver, brain and leukaemias.

10

ADMINISTRATION

Any suitable means for gastrointestinal administration (delivery) may be used. For example, the compound may be delivered orally, rectally or, indeed, by naso-gastric tube. Preferably, the compounds are administered orally.

15

For example, the composition can be administered orally in one or more of the forms of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

20

If the pharmaceutical composition is a tablet, then the tablet may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

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Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compound may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

35

Pharmaceutical formulations suitable for oral administration may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active ingredients with liquid carriers or finely divided solid carriers
5 or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration wherein the carrier is a solid are most preferably presented as unit dose formulations such as boluses, capsules or tablets each containing a predetermined amount of the active ingredients. A tablet may
10 be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compounds in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, lubricating agent, surface-active agent or dispersing agent. Moulded tablets may be made by moulding an inert liquid diluent.
15 Tablets may be optionally coated and, if uncoated, may optionally be scored. Capsules may be prepared by filling the active ingredients, either alone or in admixture with one or more accessory ingredients, into the capsule shells and then sealing them in the usual manner. Cachets are analogous to capsules wherein the active ingredients together with any accessory ingredient(s) are sealed in a rice paper envelope. The compound of
20 formula (I) or a pharmaceutically acceptable salt or ester may also be formulated as dispersible granules, which may for example be suspended in water before administration, or sprinkled on food. The granules may be packaged e.g. in a sachet.

The active ingredients may also be formulated as a solution or suspension for oral
25 administration. Formulations suitable for oral administration wherein the carrier is a liquid may be presented as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, or as an oil-in-water liquid emulsion.

The active ingredients may also be formulated as a solution or suspension suitable for
30 administration via a naso-gastric tube.

Pharmaceutical formulations suitable for rectal administration wherein, for example, the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The
35 suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in moulds.

It should be understood that in addition to the aforementioned carrier ingredients the pharmaceutical formulations for the various routes of administration described above may include, as appropriate one or more additional carrier ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like, and substances included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

CONTROLLED RELEASE

Formulations for gastrointestinal administration include controlled release dosage forms e.g. tablets wherein the active ingredients are formulated in an appropriate release - controlling matrix, or are coated with a suitable release - controlling film.

For example, in a preferable embodiment, the compounds of the invention may be administered using controlled release dosage forms. Any suitable controlled dosage form known in the art may be used in the present invention. Examples of controlled release formulations include, but are not limited to delayed release, spaced release, time coat, timed release, delayed action, programmed release, extended action, layered-time action, and repeated action controlled dosage forms. Details of suitable controlled release formulations may be found, for example, in Krowczynski, Extended-Release Dosage Forms, 1987 (CRC Press, Inc.), Chien, Novel Drug Delivery Systems, 1992 (Marcel Dekker, Inc.) and Kydonieus, Controlled Release Technologies: Methods, Theory and Applications, 1980 (CRC Press, Inc.) and US 6,174,873.

Controlled release drug delivery systems which may be used in the present invention may include, but are not limited to, feedback-regulated drug delivery systems, rate-preprogrammed drug delivery systems and activation-modulated drug delivery systems

In feedback-regulated drug delivery systems, release of drug molecules from the delivery systems may be activated by a triggering event, such as a biochemical substance, in the body. The rate of drug release is then controlled by the concentration of triggering agent detected by a sensor in the feedback regulated mechanism. In rate-preprogrammed drug delivery systems, release of drug molecules from the delivery systems are "preprogrammed" at specific rate profiles, by, for example, controlling the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. In activation-modulated drug delivery systems, release of drug molecules from the delivery systems is activated by some physical, chemical or biochemical processes and/or facilitated by the energy supplied externally.

There are a number of controlled release drug formulations that are developed preferably for oral administration. These include, but are not limited to, osmotic pressure-controlled gastrointestinal delivery systems; hydrodynamic pressure-controlled gastrointestinal delivery systems; membrane permeation-controlled gastrointestinal delivery systems; which include microporous membrane permeation-controlled gastrointestinal delivery devices; gastric fluid-resistant intestine targeted controlled-release gastrointestinal delivery devices; gel diffusion-controlled gastrointestinal delivery systems; and ion-exchange-controlled gastrointestinal delivery systems, which include cationic and anionic drugs.

Enteric coatings (for example, hydroxypropylmethylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate) may be used to coat a solid or liquid dosage form of the compounds according to the invention. Enteric coatings promote the compounds remaining physically incorporated in the dosage form for a specified period when exposed to gastric juice but to disintegrate in intestinal fluid for ready absorption.

Another type of useful oral controlled release structure, which may be used in the present invention, is a solid dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting (fusion), solvent, or melting-solvent method.

Another controlled release dosage form is a complex between an ion exchange resin and a compound according to the invention.

Other controlled release technologies that may be used in the practice of this invention are quite varied. They include SODAS (Spheroidal Oral Drug Absorption System), IPDAS (Intestinal Protective Drug Absorption System), PRODAS (Programmable Oral Drug Absorption System), and DUREDAS (Dual Release Drug Absorption System) available from Elan Pharmaceutical Technologies, Dublin, Ireland.

SODAS are multi particulate dosage forms utilizing controlled release beads. INDAS are a family of drug delivery technologies designed to increase the solubility of poorly soluble drugs. IPDAS are multi particulate tablet formation utilizing a combination of high density controlled release beads and an immediate release granulate. PRODAS is a family of multi particulate formulations utilizing combinations of immediate release and

controlled release mini-tablets. DUREDAS is a bilayer tablet formulation providing dual release rates within the one dosage form.

5 IPDAS is a multi-particulate tablet technology that is used to enhance the gastrointestinal tolerability of potential irritant and ulcerogenic drugs. Controlled release characteristics of the individual beads may avoid high concentration of drug being both released locally and absorbed systemically. By using a combination of at least two types of beads, which release their respective drugs at different parts of the intestinal tract, release of separate doses separated by a time interval may be achieved.

10 IPDAS is composed of numerous high density controlled release beads. Each bead may be manufactured by a two step process that involves the initial production of a micromatrix with embedded compounds according to the invention and the subsequent coating of this micromatrix with polymer solutions that form a rate limiting semipermeable membrane in vivo. Should a fast onset of activity be necessary, 15 immediate release granulate may be included in the tablet. A second type of granulate, which is released later may be included to provide sequential delivery of doses.

20 MODAS is a non-disintegrating table formulation that manipulates drug release by a process of rate limiting diffusion by a semipermeable membrane formed in vivo. The diffusion process essentially dictates the rate of presentation of drug to the gastrointestinal fluids, such that the uptake into the body is controlled. Because of the minimal use of excipients, MODAS can readily accommodate small dosage size forms. MODAS represents a very flexible dosage form in that both the inner core and the outer 25 semipermeable membrane may be altered to suit the individual delivery requirements of a drug. In particular, the addition of excipients to the inner core may help to produce a micro environment within the tablet that facilitates more predictable release and absorption rates. The addition of an immediate release outer coating may allow for development of products, in which separate doses of drugs may be released.

30 PRODAS is a multi particulate drug delivery system, which, may be used in the production of controlled release formulations. In this case, the incorporation of various polymer combinations within the granulate may delay the release rate of drugs from each of the individual mini tablets. These mini tablets may subsequently be coated with controlled release polymer solutions to provide additional delayed release properties. 35 One value of PRODAS technology lies in the inherent flexibility to formulation whereby combinations of mini tablets, each with different release rates, are incorporated into one dosage form. As well as potentially permitting controlled absorption of separate doses

over defined specific periods, this also may permit targeted delivery of drug to specific sites of absorption throughout the gastrointestinal tract. Combination products also may be possible using mini tablets formulated with different active ingredients.

5 DUREDAS is a bilayer tableting technology that may be used in the practice of the invention. DUREDAS was developed to provide for two different release rates, or dual release of a drug from one dosage form. The term bilayer refers to two separate direct compression events that take place during the tableting process. In a preferable embodiment, an immediate release granulate is first compressed, being followed by the
10 addition of a controlled release element which is then compressed onto this initial tablet. This may give rise to the characteristic bilayer seen in the final dosage form.

The controlled release properties may be provided by a combination of hydrophilic polymers. Hence one layer of the tablet may be formulated as an immediate release
15 granulate. By contrast, the second layer of the tablet may release the drug in a controlled manner, preferably through the use of hydrophilic polymers. This controlled release may result from a combination of diffusion and erosion through the hydrophilic polymer matrix.

20 A further extension of DUREDAS technology is the production of controlled release combination dosage forms. In this instance, two different compounds according to the invention may be incorporated into the bilayer tablet and the release of drug from each layer controlled to maximize therapeutic affect of the combination.

25 DOSE SCHEDULE

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the nature of
30 the cancer, the therapy sought, the severity of the disease, the degree of malignancy, the extent of metastatic spread, the tumour load, general health status, body weight, age, sex, and the (genetic) racial background of the patient, activity of the specific compound employed, the metabolic stability and length of action of that compound, the general health, sex, diet, mode and time of administration, rate of excretion, drug combination,
35 and the individual undergoing therapy.

As described above, according to the method of the invention, the compound having formula I as described above is administered to a mammal in need of treatment in a form

such that the compound is delivered to the site of action in two or more doses. This is achievable either by the sequential administration of two or more dosage forms of the compound separated by a time interval or by administration of a controlled release preparation which releases the two or more doses at different times.

5

The amount of each of the two or more doses of a compound of formula (I) as defined above, for example DMXAA or a pharmaceutically acceptable salt or ester thereof required to be effective as an anticancer agent according to the invention will, of course, vary and is ultimately at the discretion of the medical practitioner.

10

Preferably, the size of each dose is determined with respect to the time interval and the half-life of the compound in the plasma. For example, in one embodiment, if the plasma concentration of the compound e.g. DMXAA which causes toxicity is, say, x micromolar, a first gastrointestinal dose should cause the plasma concentration to reach less than x. After a time interval, a second dose and optionally further doses are given, said second dose (and further doses) being of sufficient magnitude to return the maximum plasma concentration to approximately the original magnitude (e.g. greater than 75%, 85% or 90% of the magnitude attained with the first dose) but still less than x. For example, in a particularly preferred embodiment, wherein the time interval corresponds to approximately one half-life, the second dose may be of approximately half the magnitude of the first (original) dose. This returns the maximum plasma concentration to the original, but it is still less than x. After a further interval of approximately one half-life, a third dose of half the original dose may be given.

25

As described in the examples, such a regime has been found to be particularly effective for gastrointestinal, e.g. oral, administration in treatment of tumours while avoiding serious toxicity and side effects. The result is particularly surprising because the toxicity associated with the oral use of drugs such as DMXAA was expected to be related to the area under the concentration-time curve (AUC) as with most other drugs and accordingly, it had been expected that the side effects associated with such a regime would have been too serious, rendering the method unacceptable. However, surprisingly, as demonstrated herein, treatment using the dose strategy of the invention is effective without causing unacceptable side effects. Without being limited to any one explanation, it is believed that the results presented herein demonstrate that the toxicity associated with compounds such as DMXAA is related to the maximum concentration and not the AUC as would be expected. This effect is also surprising because effectiveness of i.p. administration is not improved by repeat dosing.

35

Said first dose may have a magnitude which is equal, greater than or less than one or all of said further doses. Each unit dose may be of equal or different amount from other further doses. In a preferred embodiment, the first dose is greater than the subsequent dose, for example being greater than 1.5 times, for example, greater than about 2, 2.5, 3, 5, 7, or 10 times the magnitude of the subsequent dose or doses. In a particularly preferred embodiment the first dose is approximately twice the size of each subsequent dose. In a particularly preferred embodiment, said first dose is greater than 50%, more preferably greater than 60%, more preferably greater than 70%, more preferably greater than 80%, more preferably greater than 90%, more preferably greater than 95%, more preferably greater than 98% of the maximum tolerated dose when administered as a single oral dose.

In general, a suitable first dose of DMXAA for oral administration to man for treatment of cancer is in the range of 50 to 10000mg/m² of DMXAA, and, preferably, 600 to 10000 mg/m², for example from 600 to 7500 mg/m² of DMXAA, such as from 600 to 6500 mg/m² of DMXAA, suitably 1200 to 6500 mg/m² of DMXAA, particularly 2000 to 6000 mg/m² of DMXAA, more particularly 3000 to 5500 mg/m² of DMXAA, more particularly 4000 to 5500 mg/m² of DMXAA. A particularly preferred dose is in the range 4000 to 5400 mg/m² of DMXAA. A further particularly preferred dose is in the range 4500 to 5300 mg/m² of DMXAA. For example, in a preferred embodiment, the first oral dose administered is in the range 5250-5450 mg/m² of DMXAA with one, preferably two subsequent doses each in the range 2600-2725 mg/m² of DMXAA. In a particularly preferred embodiment, the first oral dose administered is the maximum tolerated oral dose (MTD) of DMXAA, which is approximately 5300 mg/m². Other suitable doses may be in the lower range, for example, from 50 to 600 mg/m².

The time interval between doses (which may be the time interval between sequentially administered separate dosage forms or the time interval between release of separate doses from a controlled release formulation) is generally greater than 1 hour, preferably, greater than 2 hours, more preferably greater than 3 hours. In a preferred embodiment, said doses are separated by a time interval of less than 24 hours, for example, 4 hours, 6 hours or 8 hours. It is to be understood that the present invention covers all combinations of suitable and preferred groups described herein above.

The present invention will now be described only by way of example and with reference to the accompanying figures, wherein:

Figure 1; Expt. I shows relative tumour volume of colon 38 tumours untreated (circle), or following treatment with DMXAA (30+15+15mg/kg orally at 4 hour intervals, triangle), Mean±SEM (standard error of the mean) of 5 mice per group.

Figure 1; Expt. II shows relative tumour volume of colon 38 tumours untreated (circle), or following treatment with DMXAA (30+15+15mg/kg orally at 4 hour intervals, triangle), DMXAA (30mg/kg single dose orally, diamond), DMXAA (15+15mg/kg at 4 hour intervals, triangle). Mean±SEM (standard error of the mean) of 5 mice per group.

Figure 2 shows the activity by oral dosing in nude mice bearing a human colon carcinoma xenograft (HT29).

EXAMPLES

Experiments 1 and 2

Materials and Methods

C57Bl/6 mice from the Animal Resource Unit, University of Auckland, were bred and housed under conditions of constant temperature and humidity, with sterile bedding and food, according to institutional ethical guidelines. All mice were aged between 8 and 12 weeks.

Drugs and Drug Administration

DMXAA was synthesized as the sodium salt (Rewcastle et al (1990) Journal of National Cancer Institute 82:528-529). DMXAA sodium salt was dissolved in sterile water and was administered orally by gavage.

Tumour growth

Colon 38 tumour fragments (~1 mm³) were implanted subcutaneously (s.c.) in the left flank of anaesthetized (sodium pentobarbital, 81 mg/kg) mice. The experiments were initiated when tumours were approximately 3-4 mm (approximately 20 mg mass) in diameter. Tumour-bearing mice were treated with drugs according to the administration schedule described before, and the tumours measured using calipers, three times weekly thereafter. Tumour volumes were calculated as $0.52a^2b$, where a and b are the minor and

major axes of the tumour, respectively. For graphical representation the arithmetic means were calculated for each time point, counting cured tumours as zero volume.

Data Analysis

Experiment I

Two groups of 5 mice were implanted with tumours. The treatment group received DMXAA according to the schedule shown, the control group received no DMXAA. The individual mice in each group were not marked, and so any one line of the spreadsheet data shown in Table 1 could be from any individual mouse of a particular group. Therefore, the spreadsheet does not show which data point is from which animal and, therefore, how much any one tumour has grown relative to its initial size.

The data were normalised, to enable plotting of the average tumour growth beginning from a relative size of 1 (see Figure 1). This was done as follows:

- all tumour sizes ($a_1, a_2 \dots a_n$) on the first day were added $=x$ (e.g. gives 78.0 for the untreated mice)
- x was divided by the number of mice (n) (e.g. $78.0/5=15.6$ for untreated mice) $=y$
- Each individual data point ($a_1, a_2 \dots a_n$) is divided by y for every day of the experiment (e.g. for first mouse in control group on first day $5.7/15.6=0.365$, on second day $23.6/15.6=1.51$ etc)

Thus, the total tumour size on the first day is 5, the average is 1, and every subsequent average of the normalised data shows average growth relative to 1.

Table 1

Actual tumour sizes for mice treated as described in Experiment I

Treatment	Tumor volume (mm ³)*														
	* 0.52 X (the minor axes) ² X major tumour axes														
Untreated	0 day	1 day	3 day	6 day	8 day										
	5.7	23.6	31.5	251.6	235.9										
	12.6	23.6	130.8	178.3	235.9										
	12.6	39.6	84.8	140.1	266.4										
	23.6	10.1	77.1	165.6	285.4										
	23.6	61.6	110.7	204.4	362.3										
30-15-15 mg/kg orally DMXAA	0 day	1 day	3 day	6 day	8 day	10 day	13 day	15 day	17 day	19 day	21 day	24 day	26 day	28 day	31 day
	6.3	18.8	6.3	6.3	0.0	14.1	4.2	0.0	0.5	0.0	0.0	0.0	0.0	150.3	373.4
	18.8	18.8	18.8	0.0	1.0	1.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	18.8	18.8	1.0	14.1	1.0	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	14.1	6.3	14.1	4.2	6.3	0.0	0.5	4.2	0.0	0.5	0.5	0.0	0.0	0.0	0.0
	14.1	18.8	14.1	14.1	6.3	1.0	4.2	0.0	0.5	0.5	1.0	6.3	41.7	0.0	0.0

Table 2

Normalised data for mice treated as described in Experiment I

Expt I normalised data																
Time		0	2	4	7	9										
Control (days)		0.36	1.51	2.02	16.13	15.12										
		0.81	1.51	8.39	11.43	15.12										
		0.81	2.54	5.43	8.98	17.08										
		1.51	0.65	4.94	10.62	18.30										
		1.51	3.95	7.10	13.10	23.22										
Time		0	1	3	6	8	10	13	15	17	19	21	24	26	28	31
30+15+15 (days)																
DNXAA		0.43	1.30	0.43	0.43	0	0.98	0.29	0	0.04	0	0	0	0	10.44	25.93
		1.30	1.30	1.30	0.00	0.07	0.07	0.00	0.04	0.00	0	0	0	0	0	0
		1.30	1.30	0.07	0.98	0.07	0.07	0.07	0.00	0.00	0	0	0	0	0	0
		0.98	0.43	0.98	0.29	0.43	0.00	0.04	0.29	0.00	0.04	0.04	0	0	0	0
		0.98	1.30	0.98	0.98	0.43	0.07	0.29	0	0.04	0.04	0.07	0.43	2.90	0	0

Experiment II

This example was performed using four groups of mice. Group 1 (control, n=5) received no treatment. Group 2 (n=5) received two 15mg/kg doses of DMXAA. Group 3 (n=5) received a single 30mg/kg dose of DMXAA. Group 4 (n=6) received three doses of DMXAA in concentrations of 30+15+15mg/kg. In this experiment tumours were all 14mm³ at the start of the experiment. Data were normalised by division by 14 to give size relative to initial size.

Table 3

Actual tumour sizes for mice treated as described in Experiment II

Treatment	Tumor volume (mm ³)*									
	0 day	3 day	5 day	7 day	10 day	12 day	14 day	16 day	17 day	18 day
Untreated	14.0	140.4	299.5	442.3	442.3					
	14.0	78.1	126.4	140.4	289.5					
	14.0	31.2	50.0	97.4	191.1					
	14.0	52.7	93.6	263.3	898.6					
	14.0	18.7	50.0	130.0	547.6					
30 mg/kg orally DMXAA	0 day	3 day	5 day	7 day	10 day	12 day	14 day	16 day	17 day	18 day
	14.0	14.0	17.6	17.6	50.0	55.3	140.4			
	14.0	48.7	48.7	58.5	91.0	152.9	347.5			
	14.0	33.3	33.3	41.6	152.9	332.7	505.4			
	14.0	23.4	50.0	91.0	91.0	332.7	623.9			
30-15-15 mg/kg orally DMXAA	0 day	3 day	5 day	7 day	10 day	12 day	14 day	16 day	17 day	18 day
	14.0	9.4	9.4	2.4	0.0	0.0	0.0			
	14.0	6.2	6.2	4.2	1.0	1.0	0.0			
	14.0	10.5	10.5	4.6	3.1	0.8	0.0			
	14.0	18.7	14.0	14.0	6.2	4.2	1.0			
15-15 mg/kg orally DMXAA	0 day	3 day	5 day	7 day	10 day	12 day	14 day	16 day	17 day	18 day
	14.0	47.3	85.9	96.7	96.7	126.4	283.3			
	14.0	14.0	31.2	31.2	37.5	112.3	249.6			
	14.0	31.2	31.2	37.5	78.1	112.3	249.6			
	14.0	58.5	112.3	172.0	274.6	274.6	546.0			
15-15 mg/kg orally DMXAA	0 day	3 day	5 day	7 day	10 day	12 day	14 day	16 day	17 day	18 day
	14.0	41.6	131.0	168.3	366.0	676.0	973.4			
	14.0	47.3	85.9	96.7	96.7	126.4	283.3			
	14.0	14.0	31.2	31.2	37.5	112.3	249.6			
	14.0	31.2	31.2	37.5	78.1	112.3	249.6			

* 0.52 X (the minor axes)² X major tumour axes

Table 4

Normalised data for mice treated as described in Experiment II

Expt.II: normalised data										
Oral	Time	0	3	5	7	10	13			
control group		1	10	21.33	31.5	31.5				
	Normalised data	1	5.56	9	10	21.33	24.89			
		1	2.22	3.56	6.94	13.61	24.89			
		1	3.75	6.67	18.75	64	81			
		1	1.33	3.56	9.26	39				
DMXAA		0	3	5	7	10	12	14	17	
	Oral 30-15-15 mg/kg	1	0.67	0.67	0.17	0	0	0	0	
		1	0.44	0.44	0.3	0.07	0.07	0	0	
		1	0.75	0.75	0.33	0.22	0.06	0	0	
		1	1.33	1	1	0.44	0.3	0.07	0	
		1	1	1	1	0.3	0.29	0.07	0	
		1	1	1.33	1	0.3	0.3	0.07	0	
	Oral 15-15mg/kg		0	3	5	7	10	12	14	
			1	3.37	6.12	6.89	6.89	9	18.75	
		1	1	2.22	2.22	2.67	8	17.78		
		1	2.22	2.22	2.67	5.56	8	17.78		
		1	4.17	8	12.25	19.56	19.56	38.89		
		1	2.96	9.33	11.99	26.07	48.15	69.33		
	Oral 30 mg/kg		0	3	5	7	10	12	14	
			1	1	1.25	1.25	3.56	3.94	10	
			1	3.47	3.47	4.17	6.48	10.89	24.75	
		1	2.37	2.37	2.96	10.89	23.7	36		
		1	1.67	3.56	6.48	6.48	23.7	44.44		
		1	1	1.78	1.78	3.56	4.17	12.25		

Results

Experiment I

5 The tumour growth delay experiment was conducted using 2 drug regimes: untreated controls (n=5) and oral DMXAA (n=5) administered in 3 doses. The first dose (30 mg/kg), was administered at t=0 hours followed by two lower doses each of 15 mg/kg at t=4 hours and t=8 hours respectively. Tumour size was measured thrice weekly and the results normalised as described above. The results are shown in Table 1 (raw data), Table 10 2 (normalised data) and Figure 1, Expt. I (plotted as a graph).

As shown in Figure 1, Expt.I, in the control group, tumours continued to grow throughout the time-course of the experiment. In contrast, in the treatment group, average tumour size decreased throughout the first 17 days of the experiment with 4/5 15 mice cured completely within 24 days. In one animal, after initial tumour size reduction, tumour size began to increase approximately 17 days after treatment.

Experiment II

20 In this example, the tumour growth delay experiment was conducted using 4 drug regimes: untreated controls (Group 1, n=5); two 15mg/kg doses of DMXAA separated by a 4 hour interval (Group 2, n=5); a single 30mg/kg dose of DMXAA (Group 3, n=5); three doses of DMXAA in concentrations of 30+15+15mg/kg administered at t=0, 4 and 8 hours respectively (Group 4, n=6). The 30 mg/kg dose is the maximum tolerated single 25 dose Zhao et al (Cancer Chemother Pharmacol. 2002 Jan;49(1):20-6). Tumour size was measured thrice weekly and the results normalised as described above. The results are shown in Table 3 (raw data), Table 4 (normalised data) and Figure 1, Expt. II (plotted as a graph).

30 As shown in Figure 1, Expt.II, in the control group, the single dose group, the 30 mg/kg dose group and the 2x15mg/kg dose group, tumours continued to grow throughout the time-course of the experiment. In contrast, in the 30+15+15 mg/kg treatment group, average tumour size decreased throughout the first 17 days of the experiment with 6/6 mice cured completely within 17 days.

35

Therefore, in contrast to other treatment regimes, in particular a single dose at the maximum tolerated dose (MTD), the multiple dose strategy surprisingly resulted in a

very significant anti-tumour effect without the serious side effects which would be expected given the area under the concentration curve.

Experiment 3

5

Methods

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Nude mice were implanted with 5×10^6 HT29 human colon cancer cells, subcutaneously. When tumours had reached a diameter of 6-8mm, mice were randomised into groups of 5 and received either no drug (untreated controls), DMXAA (sodium salt) at a single oral dose of 28mg/kg or DMXAA (sodium salt) at oral doses of 28mg/kg followed by two additional doses of 15mg/kg 4 and 8 hours after the initial dose. Tumours were then measured using callipers every 2-3 days and volumes calculated. Comparative tumour growth curves are plotted with respect to those at the onset of treatment (relative tumour volume).

15

Conclusion

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DMXAA induces antitumour activity by the oral route against a human colon carcinoma xenograft. Maximum activity was achieved by a schedule involving an initial close maximum tolerated "loading" dose followed by two 50% of initial dose "maintenance" doses.

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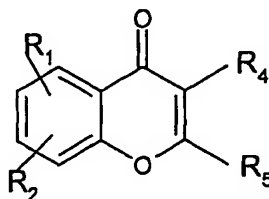
30

All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described methods uses and compositions of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in chemistry or related fields are intended to be within the scope of the following claims.

Claims

1. A method for modulating neoplastic growth, which comprises gastrointestinally administering to a mammal, including a human, in need of treatment an effective amount of a compound of formula (I):

Formula (I)



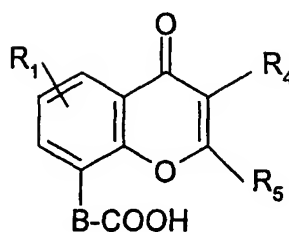
or a pharmaceutically acceptable salt or ester thereof, wherein said effective amount is delivered to its site of action in the mammal in two or more doses;

wherein:

- (a) R_4 and R_5 together with the carbon atoms to which they are joined, form a 6-membered aromatic ring having a substituent $-R_3$ and a radical $-(B)-COOH$ where B is a linear or branched substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated, and wherein R_1 , R_2 and R_3 are each independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, CF_3 , CN, NO_2 , NH_2 , OH, OR, $NHCOR$, $NHSO_2R$, SR, SO_2R or NHR , wherein each R is independently C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy; or
- (b) one of R_4 and R_5 is H or a phenyl radical, and the other of R_4 and R_5 is H or a phenyl radical which may optionally be substituted, thenyl, furyl, naphthyl, a C_1-C_6 alkyl, cycloalkyl, or aralkyl radical; R_1 is H or a C_1-C_6 alkyl or C_1-C_6 alkoxy radical; R_2 is the radical $-(B)-COOH$ where B is a linear or branched substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated.

2. The method according to claim 1 wherein the compound of Formula (I) is a compound of Formula (II):

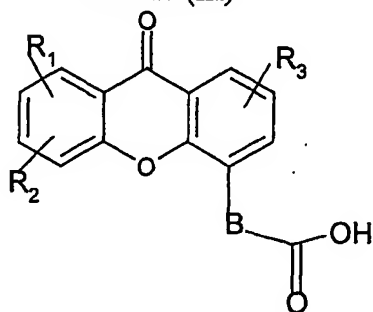
Formula (II)



wherein R_1 , R_4 , R_5 and B are as defined for formula (I) in claim 1 part (b).

3. The method according to claim 1 wherein the compound of Formula (I) is a compound of Formula (III):

Formula (III)



wherein R_1 , R_2 and R_3 are each independently selected from the group consisting of H, C_1 - C_6 alkyl, halogen, CF_3 , CN, NO_2 , NH_2 , OH, OR, $NHCOR$, $NHSO_2R$, SR, SO_2R or NHR , wherein each R is independently C_1 - C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy;

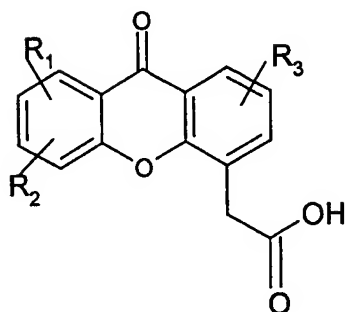
wherein B is as defined for formula (I) in claim 1;

and wherein in each of the carbocyclic aromatic rings in formula (I), up to two of the methine ($-CH=$) groups may be replaced by an aza ($-N=$) group;

and wherein any two of R_1 , R_2 and R_3 may additionally together represent the group $-CH=CH-CH=CH-$, such that this group, together with the carbon or nitrogen atoms to which it is attached, forms a fused 6 membered aromatic ring.

4. The method according to claim 3, wherein the compound of Formula (I) is a compound of Formula (IV):

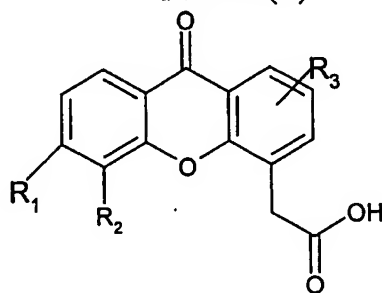
Formula (IV)



wherein R, R₁, R₂ and R₃ are as defined for formula (III) in claim 3.

5. The method according to claim 4 wherein the compound of Formula (IV) is a compound of formula (V):

Formula (V)



wherein R, R₁, R₂ and R₃ are as defined for formula IV in claim 4.

6. The method according to claim 1 wherein R₄ is H or a phenyl radical, R₅ is H or a phenyl radical which may optionally be substituted, thenyl, furyl, naphthyl, a C₁-C₆ alkyl, cycloalkyl, or aralkyl radical; R₁ is H or a C₁-C₆ alkyl or C₁-C₆ alkoxy radical; R₂ is radical - (B)-COOH where B is a linear or branched substituted or unsubstituted C₁-C₆ alkyl radical, which is saturated or ethylenically unsaturated.
7. The method according to any one of claims 1, 3, 4 or 5, wherein the compound of Formula (I) is DMXAA.

8. The method according to any one of the preceding claims wherein said compound is administered in two or more discrete dosages, separated by a time interval.
9. The method according to any of claims 1 to 7, wherein said compound is administered
5 in at least one controlled release formulation.
10. The method according to claim 9 wherein said controlled release formulation is formulated such that, in use, said formulation releases at least two discrete doses of said compound separated by a time interval.
- 10 11. The method according to claim 8 or claim 10 wherein said time interval is greater than 1 hour, more preferably greater than 2 hours, most preferably greater than 4 hours.
12. The method according to any one of the preceding claims wherein the first dose is
15 greater than the one or more subsequent doses
13. The method according to any one of the previous claims wherein the first dose is greater than 50% of the maximum tolerated dose.
- 20 14. The method according to any one of the preceding claims wherein the first dose is in the range 50 to 10000mg/m².
15. The method according to any one of the preceding claims wherein the first dose is in the range 600 to 10000mg/m².
- 25 16. The method according to claim 14 or 15, wherein the first dose is in the range 5250-5350 mg/m² with one, preferably two subsequent doses each in the range 2600-2700 mg/m².
17. The method according to any one of the preceding claims wherein the method is for
30 modulation of neoplastic growth in cancer.
18. The method according to any one of the preceding claims wherein the compound of Formula (I) is administered orally.
- 35 19. Use of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt or ester thereof for the manufacture of a medicament, for gastrointestinal administration, for the modulation of neoplastic growth, wherein, said medicament is delivered to its site of action in the mammal in two or more doses.

20. The use according to claim 19 wherein said compound is administered in two or more discrete dosages, separated by a time interval.
- 5 21. The use according to claim 19 or claim 20, wherein said medicament is a controlled release formulation.
22. The use according to claim 21 wherein said controlled release formulation is formulated such that, in use, said formulation releases at least two discrete doses of said
10 compound separated by a time interval.
23. The use according to claim 20 or claim 22 wherein said time interval is in the range 1 to 6 hours.
- 15 24. The use according to any one of claims 19 to 23 wherein the first dose is greater than the one or more subsequent doses
25. The use according to claim 24 wherein the first dose is greater than 50% of the maximum tolerated dose.
- 20 26. The use according to any one claims 19 to 23 wherein the first dose is in the range 4000 to 5400mg/m².
27. The use according to any one of claims 19 to 26, wherein the first dose is in the range
25 5250-5450 mg/m², with one, preferably two subsequent doses each in the range 2600-2725 mg/m² of DMXAA.
28. The use according to any one of claims 19 to 27 wherein the compound of Formula (I) is for oral administration.
- 30 29. A pharmaceutical formulation comprising a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt or ester thereof wherein said pharmaceutical formulation is adapted for gastrointestinal, preferably oral, administration.
- 35 30. A pharmaceutical formulation according to claim 29 wherein the compound of formula (I) is DMXAA.

31. The pharmaceutical formulation according to claim 29 or claim 30, wherein said formulation is adapted for delivery of the active compound to its site of action in a mammal in need thereof, in two or more doses, preferably two or more discrete doses, separated by a time interval.

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32. The pharmaceutical formulation according to claim 31 wherein said formulation is a controlled release formulation.

33. The pharmaceutical formulation according to claim 32 wherein, on administration to a mammal, the compound is released in two or more discrete doses separated by a time interval.

34. A process for the preparation of a pharmaceutical formulation according to claim 32 or 33 wherein said process comprises bringing into association a first unit dose of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt or ester thereof with at least one further unit dose of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt or ester thereof and one or more pharmaceutically acceptable carriers therefor wherein, on administration to an individual, said first unit dose and said further unit doses are released from the formulation in discrete doses separated by a time interval.

35. A kit comprising in combination for separate or sequential use in modulating neoplastic growth, a first unit dose of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt or ester thereof and a second unit dose of said compound of formula (I) or pharmaceutically acceptable salt or ester thereof, wherein said first and second unit doses are for oral administration in separate or sequential discrete doses separated by a time interval.

36. The kit according to claim 35 wherein the compound of formula (I) is DMXAA.

37. The pharmaceutical formulation according to any one of claims 29 to 33, the process according to claim 34, or the kit according to claim 35 or claim 36, wherein the time interval is in the range 1 to 6 hours.

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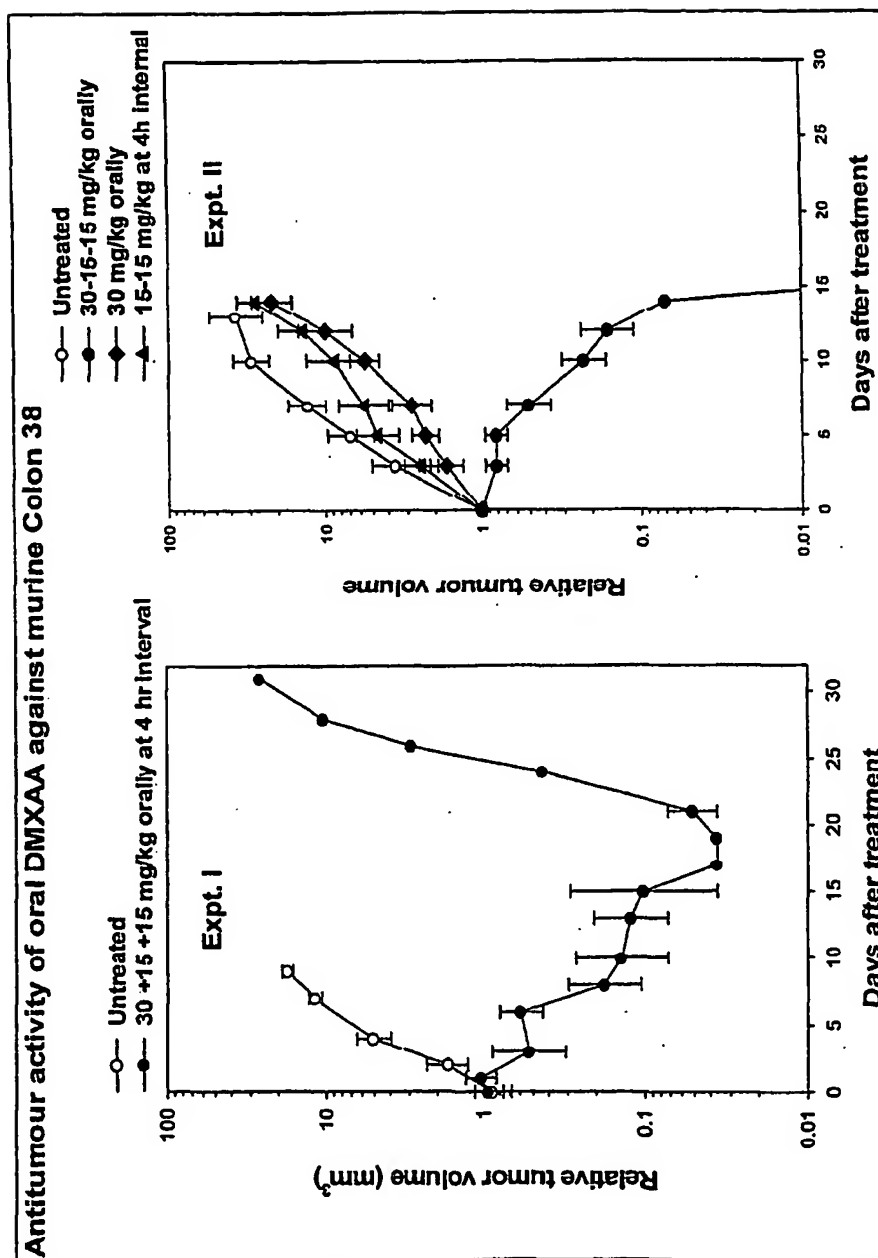
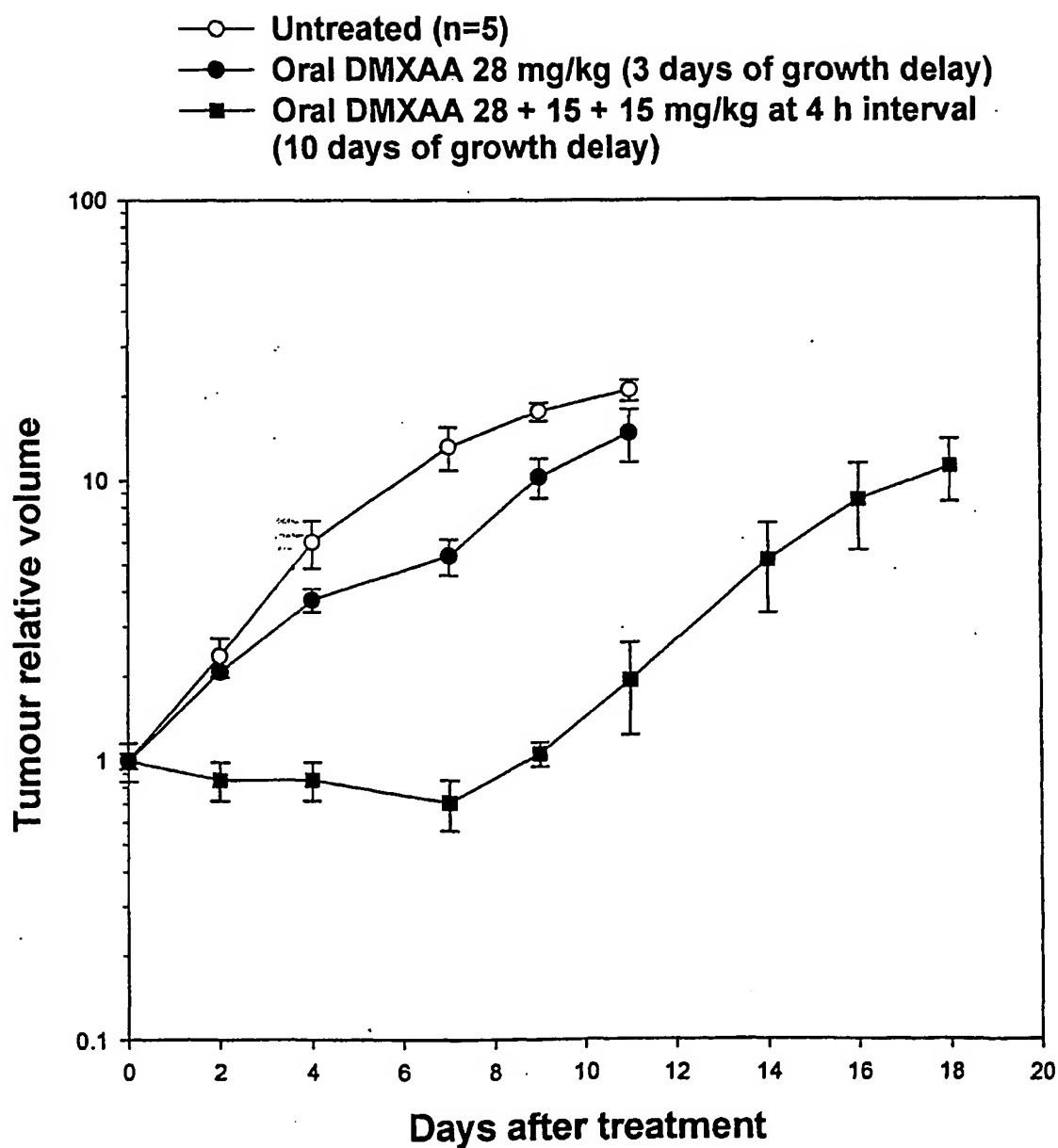


FIGURE 1

FIGURE 2



INTERNATIONAL SEARCH REPORT

PCT/GB 03/04688

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/352 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 278 176 A (DFC NEW ZEALAND LIMITED) 17 August 1988 (1988-08-17)	1-37
Y	page 26, lines 2-12; claim 10	1-37
X	ZHAO, LIANGLI ET AL: "Oral activity and pharmacokinetics of 5,6-dimethylxanthenone-4-acetic acid (DMXAA) in mice" CANCER CHEMOTHERAPY AND PHARMACOLOGY , 49(1), 20-26 CODEN: CCPHDZ; ISSN: 0344-5704, 10 November 2001 (2001-11-10), XP0001179279	1-8, 17-22, 28-31, 34-37
Y	abstract	1-37

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

10 February 2004

Date of mailing of the international search report

17/02/2004

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INTERNATIONAL SEARCH REPORT

PCT/GB 03/04688

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/04688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0278176	A	17-08-1988	AT 102616 T 15-03-1994
			DE 3789299 D1 14-04-1994
			DE 3789299 T2 04-08-1994
			EP 0278176 A2 17-08-1988
			ES 2061518 T3 16-12-1994
			HK 1000801 A1 01-05-1998
			JP 2672101 B2 05-11-1997
			JP 63295570 A 01-12-1988
			US 5281620 A 25-01-1994

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- (74) Agents: **TANNER, James, Percival et al.**; D Young & Co, 21 New Fetter Lane, London EC4A 1DA (GB).
- (21) International Application Number: **PCT/GB2003/004688**
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- (22) International Filing Date: 30 October 2003 (30.10.2003)
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- (71) Applicant (*for all designated States except US*): **CANCER RESEARCH TECHNOLOGY LIMITED** [GB/GB]; Sardinia House, Sardinia Street, London WC2A 3NL (GB).
- (72) Inventors; and
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- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 2004/039363 A1

(54) Title: **ANTI-CANCER COMPOSITION COMPRISING DMXAA OR RELATED COMPOUND**

(57) Abstract: The present invention relates to the use of compounds such as compounds of the xanthenone acetic acid class such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA) for the treatment of cancer, wherein the compounds are administered gastrointestinally, preferably orally. More particularly, the invention is concerned with the use of such compounds, wherein the compound is delivered to the site of action in the patient to be treated in two or more doses.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/04688

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/352 A61P35/00

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

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Y	abstract	1-37



Further documents are listed in the continuation of box C.



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E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

10 February 2004

Date of mailing of the international search report

17/02/2004

Name and mailing address of the ISA

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Herrera, S

INTERNATIONAL SEARCH REPORT

PCT/GB 03/04688

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/04688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0278176 A	17-08-1988	AT 102616 T	15-03-1994
		DE 3789299 D1	14-04-1994
		DE 3789299 T2	04-08-1994
		EP 0278176 A2	17-08-1988
		ES 2061518 T3	16-12-1994
		HK 1000801 A1	01-05-1998
		JP 2672101 B2	05-11-1997
		JP 63295570 A	01-12-1988
		US 5281620 A	25-01-1994
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